Key paediatric messages from the 2017 European Respiratory Society International Congress

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Abstract: In this article, the group chairs of the Paediatric Assembly of the European Respiratory Society (ERS) highlight some of the most interesting findings presented at the 2017 ERS International Congress, which was held in Milan, Italy.

DOI: https://doi.org/10.1183/23120541.00165-2017

HHS Public Access

Author manuscript

J Allergy Clin Immunol Pract. Author manuscript; available in PMC 2017 January 01.

Published in final edited form as:

J Allergy Clin Immunol Pract. 2016 ; 4(1): 1–8. doi:10.1016/j.jaip.2015.10.003.

Management of preschool children with recurrent wheezing: lessons from the NHLBI's asthma research networks

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Abstract

Recurrent wheezing in the preschool children is a common clinical problem, often associated with significant morbidity related to acute episodes. The management of these children has been complicated by a paucity of high quality clinical trials in this age group. To fill this knowledge gap, the NHBLI's asthma research networks have performed a series of clinical trials in an effort to provide practitioners with guidance on appropriate management strategies. These studies establish daily inhaled corticosteroids (ICS) in toddlers at high risk for subsequent asthma as an effective approach for the prevention of exacerbations and symptom reduction, but without evidence of disease-modifying properties. Additional studies have confirmed substantial heterogeneity in ICS response, both in terms of efficacy and effect on linear growth. Treatment with intermittent high dose ICS was demonstrated to be an alternative approach to daily low dose ICS for preventing severe episodes in toddlers with intermittent but significant wheeze and a positive modified asthma predictive index. This review details the findings and clinical implications derived from these studies, discuss the utility of biomarkers and the role of oral corticosteroids during acute exacerbations, and summarizes ongoing clinical trials in this age group.

Keywords

Asthma; wheezing; preschool children; inhaled corticosteroids; oral corticosteroids

Approximately 50% of children experience a wheezing illness during the first six years of life[1, 2], and approximately one-third of young children from the US and Europe experienced multiple days troubled by cough, wheeze or breathlessness over the preceding six winter months[3]. The morbidity and health care utilization for these wheezing episodes in preschool-aged children are disproportionately high, including a 50% greater rate of ambulatory visits,

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nearly twice the rate of emergency department (ED) visits, and nearly three-times the rate of hospitalization compared to older children[4].

Management decisions are complicated by a paucity of high quality clinical trials in preschool children. Given this knowledge gap, the NHBLI's Childhood Asthma Research and Education (CARE) Network (1999–2009) and AsthmaNet (2009–present) have focused on conducting clinical trials in preschool children in an effort to provide practitioners with guidance on appropriate management strategies. This review summarizes the findings and clinical implications derived from studies done by these two networks among preschool children with recurrent wheezing episodes.

Early life wheezing phenotypes

Over the past 20 years, numerous studies have confirmed the clinical heterogeneity of early life wheezing in terms of temporal patterns (age of onset and resolution), risk factors (personal atopy, familial atopy, environmental exposures, intrauterine factors, genetic predisposition), and long-term outcomes of these phenotypes[5].

The CARE Network's first clinical trial, the Prevention of Early Asthma in Kids (PEAK) trial[6] focused on the possibility that early treatment with inhaled corticosteroids (ICS) in preschool children at high risk for asthma could alter the progression from recurrent wheezing to asthma. In order to identify such a high risk population, the investigators used a modification of the Asthma Predictive Index (API)[7] that was developed from the Tucson Children's Respiratory Study to serve as a clinically applicable tool to identify preschool children with recurrent wheeze at high risk for subsequent asthma[6]. A positive modified API was present if the child had experienced at least 4 exacerbations of wheezing during the previous 12 months lasting more than 24h and the following major or minor criteria: one of the major criteria (parental physician diagnosed asthma, physician diagnosed atopic dermatitis, or sensitization to ≥1 aeroallergen) or two minor criteria (wheezing unrelated to colds, peripheral blood eosinophils ≥4%, or sensitization to milk, egg or peanut). Children with persistent symptomatic asthma were excluded. Detailed characterization of the 285 children enrolled in the PEAK trial demonstrated a high prevalence of atopic features[8], with the majority of the children (60%) having evidence of sensitization to food and/or aeroallergens. Male children were significantly more likely to be sensitized to aeroallergens, have a blood eosinophil levels of 4% or greater, or a total serum IgE level of greater than 100 IU/mL.

A common pattern of illness in early life is recurrent severe episodes of wheezing separated in time by periods of asymptomatic wellness, and has been termed severe intermittent wheezing[9]. 238 preschool children participated the CARE Network's Acute Intervention Management Strategies (AIMS) trial, which targeted children with recurrent episodes of severe wheezing with minimal-to-no wheezing outside of periods of acute respiratory tract illness/infection. The intermittent nature of this phenotype was reflected by infrequent activity limitation among these children (95% reported limitation fewer than twice per month), and infrequent symptoms during the 2-week study run-in period. In contrast, when episodes of wheezing did occur, they were frequent (71% experienced 4 or more episodes in

the prior year), led to health care utilization (95% with at least 1 primary care visit), ED visits (40%), hospitalization (8% over the past year), and oral corticosteroid use (median of 1 course/child over the past year), confirming the severity of episodes. Children with severe intermittent wheezing were more often males (65%). Asthma controller use was infrequent among these children, with only 35% reported any controller use in the prior year. Atopic features were frequently present, including eczema (37%) and sensitization to aeroallergens (47%). A substantial proportion (60%) of these children had evidence of risk for subsequent asthma reflected by a positive API. Within the total population, subgroups of preschool children with even more severe disease were identified - children who had received oral corticosteroids in the previous year (60% of the cohort) had higher incidences of urgent care visits and hospitalizations along with higher rates of aeroallergen sensitization and a positive API.

Prevention of acute wheezing episodes in preschool children

Given the significant morbidity and health care burden associated with wheezing episodes during the preschool years, the CARE Network conducted three trials examining various treatment approaches towards episode prevention/amelioration (Table 1.).

The PEAK trial, conducted in 285 children 2–3 years of age with a positive modified API and without significant day-to-day symptom burden, was primarily designed as an asthma prevention trial[10]. The investigators hypothesized that early use of daily ICS therapy among high-risk children might provide disease-modifying effects and decrease asthma-related symptoms after the ICS were discontinued. Children were randomized to receive either daily ICS (fluticasone propionate 88 mcg twice daily via MDI with valved holding chamber) or placebo for 2 years. After 2 years, study therapy was discontinued and the children were followed for an additional year to determine the frequency of asthma related symptoms and exacerbations. The primary outcome, the proportion of episode free days (defined as days without asthma-related symptoms or medication use) during the 3rd year of the study, did not differ between treatment groups, indicating a lack of disease modifying effect of early initiation of ICS in high risk children. However, during the 2 years of active therapy, the ICS-treated group experienced significantly more episode free days compared to placebo, along with a significant reduction in exacerbations requiring oral corticosteroids. Thus, daily low-dose ICS therapy in preschool children with a positive modified API was associated with a significant protective effect on exacerbations during the treatment period. These findings provide major support for the NAEPP/EPR3 Guideline recommendation for low dose ICS as the preferred Step 2 therapy for preschool with a positive modified API[11].

Despite the established efficacy of daily low dose ICS in increasing episode free days, parental adherence to such approaches in clinical care is suboptimal, likely due to the episodic nature of the disease in preschool children and concerns surrounding the safety of ICS therapy. Several small trials examined the potential clinical effect of either early use of oral corticosteroids or high dose ICS given at the early signs of respiratory tract illnesses among preschool children with severe, but episodic wheezing, with generally underwhelming results [12–14]. The CARE Network's AIMS trial was conducted to test the efficacy of early use of either high dose ICS or oral montelukast among preschool children

with severe intermittent wheezing[15]. In this year-long trial, 238 children were randomized to receive at the onset of specifically defined respiratory tract illnesses either high dose ICS (budesonide nebulization suspension 1mg twice daily for 7 days) or oral montelukast (4mg once daily for 7 days) or placebo, in addition to albuterol 4 times daily for 48 hours and then as needed. Study treatments were started when the participant experienced the signs or symptoms that the parents had identified as portending an impending wheezing episode. The primary outcome, the proportion of episode free days over the year, did not differ between active treatment groups and placebo, nor was there a difference in exacerbations requiring oral corticosteroids between treatment groups. In secondary analyses, participants with a positive modified API treated with either high dose budesonide or montelukast did experience modest reductions in symptom burden during respiratory tract illnesses.

Based upon the findings from the PEAK and AIMS trials, the CARE Network then conducted the Maintenance vs. Intermittent Inhaled Steroids in Wheezing Toddlers (MIST) trial to directly compare daily low dose ICS and episodic high dose ICS among 278 children 12–53 months of age with a positive modified API and at least 4 episodes of wheezing in the past year (or 3 episodes and controllers for at least 4 months in the prior year), and at least one severe asthma exacerbation requiring systemic corticosteroids, urgent unscheduled, emergent visit or hospitalization in the past year for asthma[16]. Children were randomized to receive budesonide inhalation suspension for 1 year as either an intermittent high-dose approach (1 mg twice daily for 7 days, starting early during a predefined respiratory tract illness or as a daily low-dose approach (0.5 mg nightly), with both groups receiving corresponding placebos. The primary outcome for the trial, the frequency of exacerbations requiring oral corticosteroids, did not differ between treatment strategies, nor was there a difference in day-to-day symptom burden or any other clinical outcome. The intermittent treatment group had substantially less ICS exposure over the year than the daily ICS group (150mg vs 46mg). There was no difference in linear growth between the two treatment arms. Thus, the study was unable to discern an advantage of daily ICS over intermittent high dose ICS among preschool children with a positive modified API and previous exacerbations and with a documented history of limited impairment due to asthma[16].

These three CARE Network clinical trials in preschool children at high risk for asthma, but without evidence of significant day-to-day impairment, that ICS therapy was effective in reducing exacerbations requiring oral corticosteroids, either as a daily low dose regimen or as an intermittent high dose regimen. These studies do not provide guidance to the preferred management approaches for preschool children at low risk for persistent asthma reflected by negative API status.

Early signs of impending exacerbations

As described above, intermittent treatment with high dose ICS, when provided early during the course of an evolving episode, decreases respiratory morbidity during the exacerbation. This treatment strategy relies upon parental recognition and identification of early warning signs and symptoms that precede and predict exacerbations in order to initiate the treatment early during the course of the episodes. Dr. Rivera-Spoljaric and colleagues investigated parent-reported signs and symptoms as antecedents of wheezing in preschool children in

order to determine their predictive capacity for the development of wheezing events[17]. Parents of participants in the AIMS trial[15] prospectively identified symptoms at the start of respiratory tract illnesses that, in the past, would have typically been followed by a wheezing episode. Nasal symptoms (41%) were the most common identified symptom by parents as an antecedent for wheezing episodes. However, nasal symptoms had low sensitivity and positive predictive value for subsequent wheezing. Significant cough, which was less commonly reported than nasal symptom, was the most reliable predictor of subsequent wheezing with a specificity of 78% and a positive predictive-value of 74%. These findings reinforced that parents could identify specific signs and symptoms as antecedents of wheezing, supporting adoption of this approach in subsequent clinical trials of the CARE Network and AsthmaNet utilizing individualized asthma actions plans that include parent-reported symptom patterns as the trigger for initiation of study therapies.

Biomarkers as predictors of acute exacerbations

Biomarkers that identify children with higher risk for future asthma/wheezing exacerbations may allow for more targeted approaches for escalating therapy to prevent exacerbations. Encouraged by previous reports in the preschool age population suggesting that fractional concentration of exhaled nitric oxide (FeNO) may be an informative marker for asthma diagnosis[18, 19], we investigated whether FeNO levels, measured in a subgroup of participants enrolled in the AIMS trial[15] when the children were asymptomatic, were related to the risk of subsequent respiratory tract illness assessed over the following year[20]. The risk of respiratory tract illnesses, adjusted for multiple determinants of asthma severity and activity, was indeed significantly higher among children with baseline FeNO above the 75th percentile (24.4ppb) compared to children with lower FeNO levels[20]. In addition, FeNO levels >24ppb were associated with a greater number of positive skin tests to aeroallergens[20]. These findings were subsequently confirmed in 2 separate studies in preschool children demonstrating that FeNo levels were related to the longitudinal change in lung function and with the risk of future wheezing episodes[21, 22].

Vitamin D levels have been reported to be inversely associated with adverse asthma-related outcomes among school-age children and adolescents[23, 24]. As limited data were available on the importance of serum vitamin D levels among preschool children, we investigated whether serum vitamin D levels <20 ng/mL (an established deficient level) were related to an increased rate of significant wheezing exacerbations requiring OCS[25]. Serum 25-hydroxy-vitamin D levels (25-OH-VitD) were determined in samples obtained at randomization from 264 preschool children enrolled in the MIST clinical trial[16]. 18 participants were found to be vitamin D deficient, and these participants had a significantly higher mean rate of exacerbations requiring OCS compared with non-deficient participants (1.46 vs 0.93 exacerbations/child-year, p=0.035; rate ratio, 1.56; 95% CI, 1.03–2.37). Analyzed as a continuous measure, vitamin D levels were not associated with significant exacerbations, suggesting a potential threshold effect of vitamin D level on the outcome of exacerbations in preschool children: serum vitamin D levels of at least 20 ng/mL may be adequate to attenuate the risk of exacerbations, while higher levels may not provide greater benefit. As a limited number of participants were vitamin D deficient, these results should be confirmed in a population with a higher prevalence of vitamin D deficiency. In addition,

an intervention trial is required to determine whether vitamin D supplements would prevent acute exacerbations among preschool children with episodic wheeze.

Treatment of acute severe episodic wheeze

Daily treatment with ICS is recommended in the NAEPP/EPR3 Guidelines for preschool children with persistent disease (with a positive modified API) or for those preschool children who required 2 or more courses of oral corticosteroids (OCSs) over 6 months[11] as this approach decreases the rate of severe exacerbations requiring OCSs by approximately 35%[10]. Given the occurrence of severe exacerbations despite ICS therapy, it is important to define an effective treatment regimen as rescue during acute exacerbations.

The NAEPP/EPR3 Guidelines[11] recommend prescription of OCS for significant exacerbations poorly responsive to bronchodilators. Among school-aged children and adolescents, there is substantial evidence to support the efficacy of OCS as a treatment for acute asthma exacerbations[26, 27]. However there is limited evidence supporting this intervention among preschool children[28], although it is standard practice to use OCS in this young age group. At least 3 randomized trials evaluating OCS efficacy for wheezing episodes in preschool children failed to demonstrate its efficacy[29–31]., In contrast, one randomized trial, performed in the ED setting, demonstrated benefit for OCS intervention with respect to reducing the rate of hospitalization [32]. These earlier trials had substantial limitations including suboptimal compliance with the protocol in the largest outpatient study[30] and relatively mild severity of exacerbations and substantial patient heterogeneity in the inpatient study[31].

The CARE Network approached this question with a *post-hoc* analysis investigating OCS efficacy in the CARE Network AIMS and MIST cohorts of preschool children with severe intermittent wheezing[33]. Using data from the AIMS and MIST trials, we investigated the efficacy of a short course of OCS in more than 1500 outpatient episodes of significant lower respiratory tract illnesses[33]. OCS was a rescue treatment given based on protocol-defined criteria, which included presence of symptoms that did not improve after 3 albuterol treatments given every 15 minutes, or need for >6 albuterol nebulization treatments or >12 puffs of albuterol by MDI for >24 hours, or moderate-severe cough for at least 5 of the preceding 7 days, or physician discretion with specific reason documented. All analyses were adjusted for baseline disease and episode severity. The results obtained in the initial cohort (the AIMS clinical trial[15]) showed that OCSs did not reduce symptom severity measured by symptom scores during the acute episodes, and also did not accelerate clinical recovery measured by the time to resolution of symptoms[33]. The results were confirmed in a validation cohort (the MIST clinical trial[16]), which included only preschool children with a positive modified API[6]. These findings provide post-hoc evidence that many preschool children with episodic wheeze may not benefit from OCS treatment. However, based on the *post-hoc* nature of the study, these results should not be directly translated to patient-care recommendations. Furthermore, there is an urgent need for a randomized trial that will investigate OCS efficacy in preschool children, particularly focusing on outpatient episodes and identifying if there are subgroup(s) of patients such as atopic or older preschool children, who may respond differently to OCS.

Heterogeneity of ICS response: prevention of exacerbations and potential growth effects

A meta-analysis investigating the efficacy of daily ICS therapy for the prevention of acute exacerbations in preschool children with episodic wheeze/asthma concluded that ICS treatment resulted in fewer exacerbations requiring OCS and improvement in respiratory symptoms[34]. Treatment response was greater in studies with the inclusion criteria of asthma, rather than in studies that have used the inclusion criteria of intermittent wheezing. Moreover, there was substantial variability in ICS response between the trials, potentially a consequence of different asthma/wheezing phenotypes in early life. Since some of these phenotypes may have different responses to ICS, it would be helpful to define characteristics of preschool children who respond to ICS therapy. Therefore, we investigated if there were characteristics of preschool children that identified those most likely to benefit from ICS therapy among the participants of the PEAK trial, which demonstrated that daily ICS treatment was associated with a reduction in OCS need and with an improvement in symptoms during the treatment period[10]. The following 3 domains were associated with a favorable response to daily ICS treatment evident by higher number of episode free days and/or fewer exacerbations requiring OCS: 1) demographics: boys, whites, 2) more substantial disease burden as reflected by ED visits or hospitalization within the past year or higher frequency of asthma symptoms during the study run-in period, and (3) allergy features such as aeroallergen sensitization and elevated IgE levels. These findings suggest that ICS are most likely to produce favorable responses in preschool children who have these characteristics and otherwise meet criteria for daily ICS treatment as recommended by asthma guidelines. It is noteworthy that the characteristics associated with ICS response were also reflected in a greater disease burden in general, and thus identified children with the greatest potential to improve. However, the *post-hoc* nature of these findings should not lead to withholding ICS treatment from preschool children without these specific characteristics.

In addition to the heterogeneity in favorable clinical responses described above, heterogeneity is also evident in terms of the potential for ICS-related side effects, and more specifically the impact of ICS on linear growth. The PEAK clinical trial[10] provided an excellent opportunity to explore short and long term ICS effects on linear growth in preschool children, as participants were treated with ICS (fluticasone propionate 176 mcg/day) or placebo for 2 years, and then were observed for an additional 2 years. The initial observation on the effect of ICS on growth in this cohort was a 1.1-cm reduction in height gained at the end of the 2 years of treatment, caused by a delay in linear growth, compared with those treated with placebo[10]. However, after discontinuation of fluticasone therapy in the following year, between-group differences were no longer significant because of an increase in linear growth in the ICS-treated group[10]. However, follow-up over an additional year revealed that preschool children with low initial weight were more susceptible to short and long-term effects of ICS therapy on linear growth[35]. Children who were 2 years of age and weighed less than 15 kg at enrollment demonstrated significantly less linear growth during the two years of fluticasone treatment compared with the placebo group (height difference 1.3 cm) and these between group differences in height remained significant 2

years after treatment discontinuation (height difference 1.6 cm). In contrast, linear growth was not significantly different 2 years after treatment discontinuation in younger children of greater weight or older children of any weight. The authors estimated that 10mcg/kg/day of fluticasone propionate may represent the upper limit dose to avoid the potential long-term effects of daily ICS use on growth in children 2 to 3 years of age[35]. This was the first study to suggest that ICS linear growth effects in some preschool children may be less reversible, and reinforces the principle of using the lowest ICS dose that provides clinical benefit, and discontinuing ICS therapy in preschool children who do not respond.

Studies in progress

The NHLBI's current multicenter asthma clinical research network, AsthmaNet, continues to investigate early life asthma and is conducting 3 clinical trials in the preschool population. These trials have been completed and the results should be available over the next year. These trials include:

1. The Effect of Early Administration of Azithromycin in Preventing Severe Lower Respiratory Tract Illnesses in Preschool Children (APRIL) trial. This trial evaluated if early administration of azithromycin, started prior to the onset of severe lower respiratory tract symptoms, in preschool children with recurrent severe lower respiratory tract illnesses, can safely prevent the progression of these episodes to significant episodes requiring OCS. Study population included 607 preschool children with a history of significant episodic wheezing. (ClinicalTrials.gov NCT01272635)
2. The Individualized Therapy for Asthma in Toddlers (INFANT) trial. This trial compared 3 treatment approaches on asthma symptom control and exacerbations: daily inhaled corticosteroid (ICS), daily oral leukotriene antagonist, and as needed ICS whenever albuterol was used for symptoms. The study also investigated whether differential treatment response is related to pre-defined patient characteristics. Study population included 230 preschool children with asthma. (ClinicalTrials.gov NCT01606306)
3. The Acetaminophen versus ibuprofen in children with asthma (AVICA) trial. This trial investigated if acetaminophen use is associated with asthma morbidity. This study was linked in a factorial manner to the INFANT trial (above); hence the study population is the INFANT study population. (ClinicalTrials.gov NCT01606319)

Summary

Recurrent wheezing in the preschool age group remains a challenging clinical problem. Research supported by the NHLBI's asthma research networks over the past 15+ years, along with substantial contributions from other investigative groups, has advanced the knowledge base for treatment in this age group (Table 2). These studies highlight the necessity of age-group specific trials rather than extrapolation from studies in older children and provide practitioners with high quality evidence to guide treatment decisions.

Acknowledgments

Source of funding: No financial support was provided for this manuscript.

Abbreviations

AIMS	Acute Intervention Management Strategies
API	Asthma Predictive Index
CARE	Childhood Asthma Research and Education
EFD	Episode free days
FeNO	fractional concentration of exhaled nitric oxide
ICS	Inhaled corticosteroids
Infant	Individualized Therapy for Asthma in Toddlers
MIST	Maintenance vs. Intermittent Inhaled Steroids in Wheezing Toddlers
OCS	Oral corticosteroids
PEAK	Prevention of Early Asthma in Kids
RTI	Respiratory tract illness
25-OH-VitD	25-hydroxy-vitamin D

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Table 1

Clinical trials of the NHBLI's Childhood Asthma Research and Education (CARE) Network investigating the management of preschool children with recurrent wheezing

Name of trial/Reference	Aim of the trial	Participants/Treatment arms	Inclusion Criteria	Exclusion Criteria	Main results
Prevention of Early Asthma in Kids (PEAK) trial [10]	To investigate if the use of daily low-dose ICS therapy for 2 years among toddlers at high risk for subsequent asthma would reduce asthma symptom burden after its discontinuation	• 285 children 24–48 months of age with a positive modified API and without significant day-to-day symptom burden • Randomized to receive daily inhaled fluticasone 88 mcg BID or placebo for 2 years • After 2 years, study therapy was discontinued and the children were followed for an additional year to investigate if prolonged ICS therapy has disease-modifying properties	• 24–48 months of age at randomization • Positive modified API* • Provision of written informed consent • Up to date on immunizations	• ICS use for ≥4 months in past year • ≥4 courses of OCS in past year • Ever received immunotherapy, IVIg or immunosuppressant • Life threatening asthma episode with hypoxic seizure or requiring intubation or mechanical ventilation • Chronic lung disease of prematurity, cystic fibrosis or other lung disease • Prematurity (≤35 weeks gestational age) • Oxygen use for more than 5 days in neonatal period or need for mechanical ventilation at any time • Significant developmental delay or failure to thrive • Systemic illness other than asthma • During 28 day screening period: symptoms and/or albuterol use on >4 days/ week on average or controller medication use or asthma related hospitalization, or diary completion on <22 days	• Lack of disease modifying effect of early initiation of ICS therapy: the proportion of episode free days during the 3rd year of the study did not differ between treatment groups • During the 2 years of active therapy, the ICS-treated group had significantly more episode free days relative to placebo, and a significant reduction in the rate exacerbations requiring OCS
Acute Intervention Management Strategies (AIMS) trial [15]	To investigate the efficacy of early use of either high dose ICS or oral montelukast for the prevention of significant	• 238 children, 12–59 months of age, with intermittent wheezing, and minimal (or no) daily asthma symptoms • Randomized to receive either high dose inhaled budesonide (1mg BID	• 12–59 months of age • At least 2 episodes of wheezing in the context of RTI in the past year (1 within past 6	• >6 courses of OCS in past year • >2 hospitalizations for wheezing • Use of asthma controller medications for ≥4 months in	• The proportion of episode free days over the year did not differ between active treatment groups and placebo, nor was there a difference

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	exacerbations requiring OCS exacerbations requiring OCS	for 7 days) or oral montelukast (4mg Q day for 7 days) or placebo • Study treatments were started when the participant experienced the signs or symptoms that the parents had identified as portending an impending wheezing episode	months, 1 documented by health care provider) • 2 urgent care visits for wheezing, 2 episodes requiring OCS, or 1 episode of wheeze requiring urgent care and 1 episode requiring OCS	past year or within preceding 2 weeks • Birth <36 weeks gestational age • Other significant lung disease or medical conditions • Gastroesophageal reflux under medical therapy • Current antibiotic use for sinusitis • History of life-threatening wheezing episode • During 2 week run-in period: parents completed diary cards on <80% of days, if asthma controller medications were used, or if the score for albuterol use, wheezing, difficulty breathing, nighttime cough, or asthma symptoms interfering with activities was ≥1 or if the daytime cough score was > 2 on an average of ≥4 days per week	in exacerbations requiring OCS between treatment groups • Participants with a positive modified API experienced reductions in symptom burden during the respiratory tract illnesses
Maintenance Versus Intermittent Inhaled Steroids in Wheezing Toddlers (MIST) trial [16]	To compare the efficacy of daily low dose ICS and episodic high dose ICS for the prevention of significant exacerbations requiring OCS	• 278 children, 12–53 months of age, with intermittent wheezing, and minimal (or no) daily asthma symptoms, a positive modified API, and at least 1 significant wheezing episode in the past year • Randomized to receive either inhaled budesonide as either an intermittent high-dose approach (1 mg BID for 7 days, starting early during a predefined respiratory tract illness) or a daily low-dose approach (0.5 mg Q day)	• 12–53 months of age • ≥4 episodes of wheezing (or ≥3 episodes and controller use for ≥3 months) in past year • Positive modified API • ≥1 exacerbation requiring OCS, urgent or emergency care or hospitalization in past year	• >6 courses of OCS in past year • >2 hospitalizations for wheezing • OCS use in the preceding 2 weeks • Current antibiotic use for sinusitis • Clinically relevant gastroesophageal reflux • Inability to cooperate with nebulizer therapy • Birth <34 weeks gestational age • Significant developmental delay or failure to thrive • Systemic illness other than asthma	• The frequency of exacerbations requiring oral corticosteroids did not differ between the 2 treatment groups, nor was there a difference in day-to-day symptom burden or any other clinical outcome • The intermittent treatment group had substantially less ICS exposure over the year than the daily ICS group (150mg vs 46mg)

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				• Immunodefieincy distorder • History of life-threatening wheezing episode including mechanical ventilation or hypoxic seizure • During 2 week run-in period: asthma symptoms and/or albuterol use on ≥3 days/ week on average or ≥2 night awakenings due to asthma, inadequate adherence (<75% of days) to diary card completion or nebulizer medication sue, and use of any asthma medication other than as needed albuterol	

ICS: Inhaled corticosteroids

API: Asthma Predictive Index

OCS: oral corticosteroids

RTI: respiratory tract illness

Table 2

Key messages from the NHBLI's Childhood Asthma Research and Education (CARE) Network clinical trials investigating the management of preschool children with recurrent wheezing

Severe intermittent (episodic) wheezing is a common early life phenotype of wheezing characterized by high morbidity during acute exacerbations, and minimal (or no) respiratory symptoms between these exacerbations.
Preschool children with a history of episodic wheezing, who are at high risk for asthma (based on a positive modified API), but without evidence of day-to-day impairment, have improved clinical courses in terms of exacerbations requiring OCS when they receive ICS therapy, either as a daily low dose regimen or as an intermittent high dose regimen given early during a predefined respiratory tract illness.
Serum vitamin D and FeNO levels may serve as biomarkers that identify children with higher risk of future exacerbation; this may allow for more targeted approaches for therapy in order to prevent exacerbations.
ICS response among preschool children with episodic wheezing is heterogonous. Children with atopic manifestations and with greater disease burden may experience greater ICS response.
2-year-old children who weigh less than 15 kg may be more susceptible to growth effects from daily low dose ICS, which may be less reversible. Therefore, when using a daily ICS treatment approach in children 2 to 3 years of age, it is recommended not to exceed the equivalent of 10mcg/kg/day of fluticasone propionate in order to minimize the risk of potential long-term effects on growth.
The role of OCS in the treatment of acute episodic wheeze in preschool children is yet to be conclusively determined.
Results of additional clinical trials will hopefully provide evidence to fill the current gaps in our knowledge on the management of preschool
children with wheezing and asthma.

FeNO: fractional concentration of exhaled nitric oxide

ICS: Inhaled corticosteroids

API: Asthma Predictive Index

OCS: oral corticosteroids

J Allergy Clin Immunol Pract. Author manuscript; available in PMC 2017 January 01.